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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,133	02/11/2004	J. Michael Ruppert	D6236CIP2	5751

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ATLANTA, GA 30309-3915

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/776,133	RUPPERT ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-7,11-13 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-7, 11-13, 32 and 33* is/are rejected.

7)☐ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants election with traverse of the invention of Group I. The traversal is on the grounds that it would not be an undue burden for the examiner to search all of the instant claims. This has been considered but not found persuasive. The pending claims were divided into six groups by the restriction requirement, each group covering differing classifications. Based on this difference in classification, restriction for examination purposes is deemed proper and adhered to. The restriction requirement is thus made FINAL. ...

Claims 1-40 are pending. Claims 8-10, 14-31 and 35-40, drawn to nonelected inventions, are withdrawn from consideration. Claims 1-7, 11-13 and 32-34 are examined on the merits.

Priority

Acknowledgement is made to applicants claim to an earlier effective filing date through 09/572,224, filed May 17, 2000. Review of said application indicates a lack of support for determining prognosis of breast cancer by measuring GKLF/KLF4 or monitoring of an treatment effectiveness by measuring localization of the GKLF/KLF4. The '224 application states on page 63, lines 2-7,

For uninvolved epithelium, DCIS, and invasive carcinoma alike, the average cytoplasmic staining was 1.8-2.5 fold greater than nuclear staining, suggesting that subcellular localization was not altered during tumor progression in any consistent fashion.

Further, no mention is made in the '224 application of linking prognosis to the intracellular location of GKLF/KLF4. It is noted tat the '224 application was filed with claims 25-27 which are identical to the instant claims 11-13 of the instant specification with the exception of reliance on the instant antibody of claim 11. However, for the reasons stated above, claims 25-27 do not provide support for the instant claims because the '224 specification fails to address the subcellular localization of the GKLF/KLF4 protein which is required for the enablement of the claims. It is further noted that the antibody relied upon in the '224 application (claim 24) does not provide support for the antibody relied upon for the instant claim 11 because one f skill in the art could not envisage the antibody used in claim 11 by either the disclosure of the '224 application.

Acknowledgement is made to applicants claim to an earlier effective filing date through 10/194,527, filed July 12, 2002. Review of said application indicates a lack of support for determining prognosis of breast cancer for any patient by measuring GKLF/KLF4 or monitoring of an treatment effectiveness by measuring localization of the GKLF/KLF4. It is noted that claims 21-23 and 25-27 of the '527 application encompass the instant claims with the exception of the reliance on the instant antibody of claim 11. The '527 application states on page 71, lines 1-3 that

Current studies are aimed at determining survival rates in groups with distinct nuclear/cytosolic ratios of KLF4.

and on page 70, lines 10-16, which state that KLF4 expression in breast tumors can be grouped into three distinct patterns including 1. predominantly cytosolic, 2. predominantly nuclear or 3. mixed, with the "mixed" pattern being the most common, and that for the first category of predominantly cytosolic staining, 70% of patients with greater than median cytosolic staining survived for 5 years or more versus 60% of patients with less than median cytosolic staining.

This fails to provide support for determining the prognosis of patients in the categories of 2. predominantly nuclear or 3. mixed. Further, the '527 application is mute with respect to monitoring treatment efficacy by means of detecting the localization of KLF4 for individuals suffering from oral squamous cell carcinoma, as well as for individuals suffering from breast cancer having a KLF4 expression pattern after treatment which is commensurate with 2. predominantly nuclear KLF4 expression pattern or 3. mixed KLF4 expression pattern. It is further noted that the antibody relied upon in the '527 application (claim 24) does not provide support for the antibody relied upon for the instant claim 11 because one f skill in the art could not envisage the antibody used in claim 11 by either the disclosure of the '527 application.

Thus, claims 1-7, 11-13 will be given the effective priority consistent with the instant filing date of February 11, 2004

Claims 32-34 will be given the effective filing date of 05/17/2000, consistent with the disclosure in the 09/572,224 application of the method of monitoring a response to treatment based on the expression levels of GKLF/KLF4 in a patient. It is noted that the provisional application 60/134,936 provides no disclosure on monitoring the response of a patient to treatment based on GKLF/KLF4.

Claim Objections

Claim 11 is objected to because of the following informalities: Claim 11 is dependent upon a non-elected claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is vague and indefinite in the recitation of detecting the "localization" of KLF4, because the final method step is dependent on "decreases" of the KLF4 level which address the level of the KLF4 expression but does not address the localization of the KLF4 expression.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of

direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant method claim requires the use of the monoclonal antibody IE5. In order to practice the method of claim 3, one of skill in the art must be able to make or obtain the IE5 antibody, and it is not clear if the exact cell line producing the antibodies can be made without undue experimentation. Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1, second full paragraph) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies.

If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing the identical monoclonal antibodies as described in the specification and were in the applicant's possession at the time the application was filed.
Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method indicating a greater likelihood of survival, does not reasonably provide enablement for a method indicating a greater likelihood of a response to a specific therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims require the correlation between the predominantly cytosolic versus predominant nuclear staining of an immunohistochemical sample for KLF4. The specification

teaches that predominantly nuclear staining and a lower cytosolic staining are indicative of a lower likelihood of survival and that predominately cytosolic staining is indicative of a greater likelihood of survival. The specification does not provide a correlation between the response to a specific therapy and the predominantly cytosolic or predominantly nuclear staining of a breast tumor sample, although the specification suggest response to drug administration, radiation therapy, gene therapy and chemotherapy could be correlated to such staining. Thus, it would be an undue burden on one of skill in the art to determine a correlation between the response to a specific therapy and the predominantly cytosolic or nuclear staining for KLF4.

Claims 11, 12, 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for monitoring treatment thereby evaluating the effectiveness of treatment in an individual wherein decreases in the level of KLF4 is indicative of and effective response to treatment and wherein said individual suffers from breast carcinoma or oral squamous cell carcinoma, does not reasonably provide enablement for methods for monitoring treatment thereby evaluating the effectiveness of treatment in an individual wherein decreases in the level of KLF4 is indicative of and effective response to treatment and wherein said individual suffers from any other type of affliction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 11 and 12 are drawn to a method of monitoring a treatment thereby evaluating effectiveness of the treatment in an individual, comprising the step of: administering the monoclonal antibody of claim 9 to said individual prior to, during and post said treatment, wherein said antibody detects the localization and level of Kruppel-like factor 4 (KLF4) protein, and wherein decreases of KLF4 protein level indicate effective response of said individual to said treatment, so treatment is monitored and the effectiveness of said treatment is evaluated in said individual. Claims 32 and 33 are drawn to a method of monitoring a treatment thereby evaluating effectiveness of the treatment in an individual, comprising the step of: detecting the expression levels of Kruppel-like factor 4 (KLF4) in said individual prior to, during and post said treatment, wherein decreases of said expression levels of KLF4 indicate effective response of said individual to said treatment, therefore, said treatment is monitored and the effectiveness of

said treatment is evaluated in said individual. Thus the claims encompass the monitoring of treatment in any individual having any affliction. The specification teaches that KLF4 is upregulated in both breast carcinoma relative to normal breast cells relative to normal oral squamous cells. However, the art teaches that individuals afflicted with bladder cancer, colorectal cancers and esophageal cancer (Ohnishi et al, BBRC, 2003, Vol. 308, pp. 251-256; Zhao et al, Oncogene, 2004, Vol. 23, pp. 395-402, see page 396-397 under the heading of "Results"; and Wang et al, World J of Gastroenterology, 2002, Vol. 8, pp. 966-970). Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the broadly claimed methods apart from individuals suffering from breast carcinoma or oral squamous cell carcinoma, because there is no reliable nexus between the cancerous state, or any other affliction and the overexpression of KLF4.

Claim 34 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
01/21/2007